CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022462Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-462 SUPPL # HFD #

Trade Name GABLOFEN

Generic Name baclofen

Applicant Name CNS Therapeutics

Approval Date, If Known 11/19/10

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-075 Lioresal

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Lana Chen,RPh
Title: Project Manager, DNP
Date: 2/3/11

Name of Office/Division Director signing form: Russell Katz, MD
Title: Division Director, DNP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

LANA Y CHEN
02/08/2011

RUSSELL G KATZ
02/09/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022462

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

CNS Therapeutics, Inc.
332 Minnesota Street, Suite W1750
St. Paul, Minnesota 55101

ATTENTION: John J. Foster
Chief Executive Officer

Dear Mr. Foster:

Please refer to your New Drug Application (NDA) dated March 27, 2009, received March 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baclofen Injection 0.05 mg/mL, 10 mg/20 mL (0.5 mg/mL), 40 mg/20 mL (2 mg/mL), (b) (4)

We also refer to your October 29, 2009, correspondence, received October 30, 2009, requesting review of your proposed proprietary name, Gablofen. We have completed our review of the proposed proprietary name, Gablofen and have concluded that it is acceptable.

The proposed proprietary name, Gablofen, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 29, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lana Chen at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Denise P. Toyer,Pharm.D,
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

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/s/

DENISE P TOYER
01/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-462

PDUFA GOAL DATE EXTENSION

John J. Foster
Chief Executive Officer
CNS Therapeutics, Inc.
539 Bielenberg Drive, Suite 200
Woodbury, MN 55125

Dear Mr. Foster:

Please refer to your March 27, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for baclofen intrathecal.

On December 22, 2009, we received your December 18, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 30, 2010.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely yours,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

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/s/

LANA Y CHEN
01/07/2010

RUSSELL G KATZ
01/11/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-462 **INFORMATION REQUEST**

CNS Therapeutics, Inc.
Attention: John J. Foster
539 Bielenberg Drive, Suite 200
Woodbury, MN 55125

Dear Mr. Foster:

Please refer to your March 27, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baclofen (Intrathecal) injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. (b) (4) Tighten your limits appropriately to reflect the API manufacturer's limit.

2. Provide batch analysis data for the reference standard (Baclofen), Lot # 03250814.

3. The samples of the drug solution remaining in the Medtronic pump reservoirs after the 180 day stability were tested for leachates from the (b) (4) and the study concluded that no leachates were identified at a level of concern. Provide experimental details and the other relevant information such as:
   (a) How were the potential leachable identified?
   (b) What was the nature of the detected leachable?
   (c) What was the level of concern for found leachables and how were these levels determined.
   (d) What is the limit of detection and limit of quantitation of the analytical procedure use for each potential leachable?
   (e) What analytical methods were used?

4. The RLD (reference listed drug) data provided for the pump-drug compatibility study was generated from only one lot. Therefore, the comparative study is not conclusive. Provide compatibility data from at least another two additional lots of RLD which are close to the manufacturer's expiration date.

5. We recommend that you evaluate the physical stability of the drug product inside the pump/catheter under a flow condition that simulates actual use.

6. Baclofen intrathecal injection is often used in combination with other medication such as morphine. (b) (4)

7. The provided stability data do not support the requested two (2) years shelf life. Provide additional stability data supported by appropriate statistical analysis as per ICH Q1E to support your request of expiration period extrapolation.

8. Tighten proposed osmolality range and pH range in your finished product specification based on the actual available data.

9. Some of the process variability such as achievement of dissolution of the drug substance (b) (4)

10. Describe the type of needle to be used/attached to the syringe barrel and appropriate CMC information to support its safe use with your product.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

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/s/

RAMESH K SOOD
12/07/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-462 **INFORMATION REQUEST**

CNS Therapeutics, Inc.
Attention: John J. Foster
539 Bielenberg Drive, Suite 200
Woodbury, MN 55125

Dear Mr. Foster:

Please refer to your March 27, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baclofen (Intrathecal) injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Include microbial limits and bacterial endotoxin testing for the API in the specification.
2. The drug product-device compatibility study was limited as follows:
   (i) Only one lot of the reference product was studied and only one time point for the reference product was submitted. The study should include multiple lots of the reference product and at least three time points.
   (ii) Compatibility data with Medtronic pump shows that the degradation product, (b) (4). Clarify why the product should be considered compatible in this device while the result is not within the specification.
   (iii) Provide drug product-pump compatibility for the (b) (4). We note that you performed a dilution study but it did not cover the lowest vial strength 0.5 mg/mL.
   (iv) How does the Medtronic pump interior look at the end of the study? A photograph (like the (b) (4) pump submitted in the application) should be submitted to show compatibility.
   (v) Drug product –pump catheter compatibility was not demonstrated.
   (vi) Information provided for the precipitation study with the Elliott's B solution is very limited. Provide the detailed experimental protocol and a copy of the study report.
3. Additional stability data is required to support your proposed shelf life of two years.
4. You mentioned in the original application that the extractable leachable six months data on syringes would be available on June 4, 2009 and compiled data would be provided to the Agency post submission. We have not received these data.

5. [redacted] (b) (4) Clarify the purpose of this excipient and at what stage it is used.
6. The proposed osmolality and pH range are [redacted] (b) (4) respectively for all concentrations. The ranges are too wide and should be tightened appropriately based on the actual batch data.
7. In the forced degradation studies, you have only provided the percent recovery of Baclofen from different condition; however, it is not clear what are the other [redacted] (b) (4) ? Provide explanation for the lack of [redacted] (b) (4) .
8. In your response dated August 3, 2009 to our question regarding the effect of temperature [redacted] (b) (4) Provide your supporting data.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

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/s/

MARTHA R HEIMANN
10/29/2009

From: John Foster
To: Keefe, Stephanie;
cc: Chen, Lana Y;
Subject: Re: CNS Therapeutics Type A Meeting Request NDA 22-462
Date: Monday, September 21, 2009 11:36:27 AM

Stephanie,

This is to confirm receipt of your message and to accept the meeting. We will be there in person. We may have one person who will need to join via phone. I will let you know about that asap.

THANK YOU! I sincerely appreciate your hard work to get this meeting back on the schedule. I will inform our team.

John

John J. Foster
Chief Executive Officer
CNS Therapeutics, Inc.
332 Minnesota Street, Suite W1750
St. Paul, MN 55101
651-207-6959 o 651-503-1507 c
jfoster@cnstherapeutics.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>
Date: Mon, 21 Sep 2009 10:05:44 -0500
To: John Foster <jfoster@cnstherapeutics.com>
Cc: Lana Chen <lana.chen@fda.hhs.gov>
Subject: RE: CNS Therapeutics Type A Meeting Request NDA 22-462

John,

We were able to reschedule your face to face meeting for an October date. If you prefer a Teleconference,for the same dat, please let me know as soon as possible. I have attached the new Meeting confirmation letter. Please confirm receipt of both the email and it's attachment. Thank you.

Stephanie

From: John Foster [mailto:jfoster@cnstherapeutics.com]
Sent: Friday, September 18, 2009 3:38 PM
To: Keefe, Stephanie
Cc: Chen, Lana Y; Katz, Russell G
Subject: Re: CNS Therapeutics Type A Meeting Request NDA 22-462

Stephanie,

Thank you for your email.

While I can appreciate the many demands for the time of the team members, it is frustrating that with just eight business days until our meeting the Agency is seeking to reschedule it. This meeting is vital to us and we have worked hard to meet your deadline and to provide a comprehensive briefing package to support a productive meeting.

As you know CNS Therapeutics, Inc. is a small business and this is our first NDA submission. It is our desire to establish a successful and collaborative relationship the Agency and the Division of Neurology. It has been our goal from the initiation of this product development program to deliver an exceptional NDA to the Division for review and approval. To do so we have we have worked diligently and have utilized leading scientific and regulatory experts to support us. We have also met with the Division and discussed this development program at great length. Indeed, we believe that we have met every deadline for submission, and have responded fully and in a timely fashion to all of the Agency's requests and inquiries.

Upon receiving our 74 Day letter from the Division in June, CNS promptly requested a Type A meeting. We certainly viewed the issue as one that had the potential to stall, if not derail, the development of this product. Your team responded by scheduling a Type C meeting for September 30th. Now you have requested to reschedule the meeting to November or December. Meanwhile, we have answered all of the questions that the reviewers have asked us, have submitted amendments to the NDA as requested, have passed the pre-approval inspection at our manufacturing site, and are producing process validation lots at significant financial risk. It is our impression that a resolution of the open regulatory issue in the 74-day letter is the key topic remaining. Our PDUFA date of January 30, 2010 is rapidly approaching and we are ready to complete the review. Any further delay will create significant hardship for the company and delay the supply of this valuable product to patients.

If the Agency has met internally and discussed this issue, then we respectfully request that you provide us written responses to the questions we posed in our briefing package according to the original meeting schedule - before September 30th.

If this is not the case, we respectfully request that instead of a face-to-face meeting, we schedule a teleconference meeting as soon as possible in order resolve the single open regulatory issue. We hope that a telephone meeting could be arranged in accordance with the Agency's published Guidance for Industry - Formal Meetings with Sponsors 2/00, in the next 30 days and well before the November-December period you proposed. We will accommodate any date that you identify for a teleconference between now and the end of October.

I would welcome the opportunity to visit with you or Lana by phone to discuss this topic as well. My cell phone is 651 503 1507. Please call me at any time.

Best regards,

John

John J. Foster
Chief Executive Officer
CNS Therapeutics, Inc.
332 Minnesota Street, Suite W1750
St. Paul, MN 55101
651-207-6959 o 651-503-1507 c
jfoster@cnstherapeutics.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>
Date: Thu, 17 Sep 2009 11:02:43 -0500
To: John Foster <jfoster@cnstherapeutics.com>
Subject: RE: CNS Therapeutics Type A Meeting Request NDA 22-462

John,

I wanted to provide you with an update, regarding this Meeting. The Agency is going to have to reschedule the meeting date. Key members of the review team are unable to

accommodate this date, due to prior commitments in their work schedule. Please provide me with dates, which would work for your team for the month of November and December. I hope to reschedule this meeting as soon as possible, upon receipt of your availability. Thank you for your time!

Stephanie

From: John Foster [mailto:jfoster@cnstherapeutics.com]
Sent: Tuesday, August 04, 2009 11:43 AM
To: Keefe, Stephanie
Subject: Re: CNS Therapeutics Type A Meeting Request NDA 22-462

Stephanie,

Thank your for your email. This is to confirm receipt.

John

John J. Foster
Chief Executive Officer
CNS Therapeutics, Inc.
332 Minnesota Street, Suite W1750
St. Paul, MN 55101
651-207-6959 o 651-503-1507 c
jfoster@cnstherapeutics.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>
Date: Tue, 4 Aug 2009 10:37:57 -0500
To: John Foster <jfoster@cnstherapeutics.com>
Cc: Lana Chen <lana.chen@fda.hhs.gov>
Subject: RE: CNS Therapeutics Type A Meeting Request NDA 22-462

Mr. Foster,

Please refer to your Type A Meeting Request dated July 14, 2009, received July 16, 2009. The Division has decided to grant your meeting request and have reclassified the Meeting type to a Type C Meeting. Please see the attached meeting confirmation letter for details of

your meeting. Please pay close attention to all dates and times provided. The date of the meeting was the first available date, in which all necessary attendees were available. Please confirm receipt of this email and it's attachment. Thank you for your time.

Stephanie N. Keefe

From: John Foster [mailto:jfoster@cnstherapeutics.com]
Sent: Wednesday, July 29, 2009 9:35 AM
To: Keefe, Stephanie; Chen, Lana Y
Subject: Re: CNS Therapeutics Type A Meeting Request NDA 22-462
Importance: High

Stephanie, Lana,

Thank you for your email.

The reclassification of our request to a Type C meeting is quite concerning to us. We believe our request clearly qualifies as a Type A meeting, in light of the fact that our development program will be substantially stalled if the underlying issue is not promptly resolved. Such a delay would result if the Agency maintains their initial position that our product needs to be reviewed as a drug-device combination, because CNS would need to seek out a collaborative relationship with a pump manufacturer who would be willing to supply access to its PMA.

Additionally, based on our PDUFA date, (b) (4) Moving forward with process validation batches without direction and resolution of our concerns about the drug-device designation raised in the 74-day letter would put our investment in the manufacture of process validation batches at substantial risk. I'm confident that you can appreciate that as a small business we are willing to make this type of investment under the assumption that these batches will ultimately be marketable. The absence of a timely resolution of the underlying issue in the 74-day letter would render these batches non-marketable, as they would have little or no remaining shelf life at the time of approval.

We are confident that the Agency appreciates the importance of a timely resolution of this issue in light of our mutual goal of an NDA approval by the January 30, 2010 PDUFA date. We also recognize that you have many requests for your time. However, since the Division did not raise the issue of a drug-device designation during our Pre-NDA meeting, or in any related correspondence, we

believe that we are entitled to have our meeting scheduled as a matter of high priority, as is the case with Type A meetings. Accordingly, we respectfully request that the Division give us a meeting date as soon as possible. We remain ready to meet as soon as you can assemble the appropriate team members.

Thank you and best regards,

John

John J. Foster
Chief Executive Officer
CNS Therapeutics, Inc.
332 Minnesota Street, Suite W1750
St. Paul, MN 55101
651-207-6959 o 651-503-1507 c
jfoster@cnstherapeutics.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>
Date: Tue, 28 Jul 2009 12:19:22 -0500
To: John Foster <jfoster@cnstherapeutics.com>
Cc: Lana Chen <lana.chen@fda.hhs.gov>
Subject: FW: CNS Therapeutics Type A Meeting Request NDA 22-462

Dear John,

My name is Stephanie Keefe and I am assisting Lana with this Meeting Request. I wanted to send you an email to let you know we have reclassified this Meeting Request to a Type C and are currently working on scheduling the first available meeting date. I will send you a meeting confirmation email, with details of your meeting, when they are available. Thank you for your time.

Stephanie N. Keefe

From: John Foster [mailto:jfoster@cnstherapeutics.com]
Sent: Tuesday, July 14, 2009 12:48 PM
To: Chen, Lana Y
Subject: CNS Therapeutics Type A Meeting Request NDA 22-462

Importance: High

Dear Lana,

Attached please find the Type A meeting request I mentioned in our recent communication. It is formatted and bookmarked as an electronic document for submission. Three hard copies will be sent via Federal Express today as well.

We appreciate your attention to this matter and look forward to working with the Division of Neurology Products as you continue the review of our NDA.

Best regards,

John

John J. Foster
Chief Executive Officer
CNS Therapeutics, Inc.
332 Minnesota Street, Suite W1750
St. Paul, MN 55101
651-207-6959 o 651-503-1507 c
jfoster@cnstherapeutics.com

Dear Mr. Foster,

Please refer to your Type A Meeting Request dated July 14, 2009. Your meeting request refers to NDA 22-462.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting to be a Type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000).
The meeting is scheduled for:

Date:	October 7, 2009
Time:	8:00-9:00 AM EST
Location:	FDA White Oak Campus; 10903 New Hampshire Ave., Silver Spring, MD; Building 22, Rm. 1417

Current Planned CDER Participants:
Russell Katz, MD, Neurology Division Director
Eric Bastings, MD, Clinical Team Leader
Rob Harris, MD, Clinical Reviewer
Martha Heimann, Ph.D., CMC Team Leader
Eric Duffy, Ph.D., Supervisory Chemist, ONDQA/DPE
Carla Cartwright, General Attorney, OCC
Margaret Renner, General Attorney, OCC
Mitch Weitzman, Regulatory Counsel, ORP/DRPI
Kimberly Dettelbach, General Attorney, OCC
Patricia Love, M.D., Medical Officer, OCP
Cindy Kortepeter, Pharm.D., Lead Pharmacist, DPV I
Laurie Kellie, PA-C, Safety Regulatory Project Manager, OSE
Charlene Flowers, Pharm.D., Pharmacist, DPV I
Lana Chen, R.Ph., Regulatory Project Manager

Visiting FDA:
Please email Lana Chen a list of your attendees 48 hours in advance of the meeting.

Be sure to include Lana as the FDA contact to call when you arrive, as all visitors must be escorted by an FDA employee at all times. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the meeting room: Lana's number, 301-796-1056; the division secretary, 301-796-2250. The FDA contact will be called to escort sponsor attendees throughout the building.

The north parking lot has been subdivided with barriers, and the area farthest from the building is designated for visitor parking. All visitors for building 21 and 22 should park in this area. The visitor portion of the lot is open from 6:00 AM - 6:00 PM Monday through Friday.

Buses or limos bearing visitors may be allowed to drop and pick up passengers in front of building 22, if prior notice is given. The drivers can move to the visitor lot and wait for their party, or they may go off-site.

WO Visitor
arking.pdf (181 KB.

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance.

Meeting Materials:

Provide your background information for this meeting (3 archival copies for the NDA file) at least one month prior to the meeting. **If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by September 3, 2009, we may cancel or reschedule the meeting.** Also, please provide 15 desk copies at the time of your archival copy submission.

Send all archival copies of your meeting package and any future communications concerning this NDA in duplicate, identified by the above NDA number, to the following address:

Archival Copies:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Desk copies can be sent directly to the RPM using overnight mail via FedEx, UPS or DHL at the following address:

Lana Chen, Regulatory Project Manager
Food and Drug Administration
White Oak CDER, Building 22, Room 4353
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, please send an electronic copy of your meeting package (Adobe pdf), including meeting questions (in WORD format) via email to myself and Lana Chen at the time of the briefing package submission.

If you have questions, please email or call myself or Lana Chen at the following:

(email: Stephanie.keefe@fda.hhs.gov; phone (301) 796-4098)
OR
(email: Lana.Chen@fda.hhs.gov; phone (301) 796-1056)

Also, please let me know if you have received this information.

Sincerely,

Stephanie N. Keefe, CSO
On behalf of Lana Chen, R.Ph.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	GI-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEPHANIE N KEEFE
09/22/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-462

John J. Foster
Chief Executive Officer
CNS Therapeutics, Inc.
539 Bielenberg Drive, Suite 200
Woodbury, MN 55125

Dear Mr. Foster:

Please refer to your March 27, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for baclofen intrathecal.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 29, 2009 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Regulatory

The Agency considers Baclofen Intrathecal Injection to be a combination product that consists of a drug component and a device component. In your application, you will need to identify a specific pump, or pumps, with which your specific drug will be delivered. Additionally, you will need to obtain, and submit, a letter of authorization from the manufacturer of each intended pump for FDA to reference the respective device PMA. Also, for approval the drug component and identified device component must have mutually conforming labeling. (See related matters under Chemistry, Manufacturing and Controls.)

Chemistry, Manufacturing and Controls

From the physicochemical compatibility study during the course of pharmaceutical development of CNS's product, it was found to be compatible with the Medtronic pump system, SynchroMed®. However, the device's approved label does not recommend using any product other than Lioresal®, (b) (4). Therefore, despite the safe compatibility with the SynchroMed pump system, the highest strength of the CNS's product would not have any approved device/pump system for chronic intrathecal administration to patients.

Further, the draft package insert states that this product should be used in any implantable pumps approved by the FDA specifically for the chronic intrathecal administration of baclofen. However, the compatibility study shows that the product has stability issue when used with J&J

Codman 3000 pump system. Therefore, appropriate instructions must be written in the label/package insert to avoid such incompatible pumps for chronic intrathecal delivery.

The equilibrium solubility of baclofen in water is reported within the NDA as (b) (4). (b) (4)

(b) (4)

(b) (4)

The acceptance limits for potency and density as listed in module 3.2.P.3.4. either have one discrete value or are "as measured". On the other hand in batch records you have stated that QC hold samples after the solubilization of the drug substances (b) (4) are taken to test appearance, pH, potency and density. There are no limits proposed for potency and density in the batch record. Clarify this discrepancy. Moreover, the acceptance limits proposed in section 3.2.3.4 for potency and density are single values rather than an acceptable range. Revise these limits to an acceptable range for these two attributes.

Please provide a rationale for setting up a particle size specification for the drug substance when it is in solution.

No photostability testing appears to have been performed on the drug product. You will need to either provide adequate justification for not performing photostability testing or perform this test.

The proposed shelf life (2 years) based on the limited stability data is not justified. Provide additional long-term stability data to justify your proposed expiration date as per ICH QA1 (R2) and ICH Q1E.

Nonclinical

In the study reports for two (Study Nos. 069-001 and 069-002) of the three nonclinical studies submitted, the information provided in the "Data Section 1" portion of each report is unreadable. These sections will need to be provided in a readable format.

Microbiology

We note that container closure studies were submitted for vials, with a notation that the syringe container closure study was pending. The syringe container closure study would need to be submitted prior to approval for this application.

Labeling

Please provide the proposed label as an annotated Word file.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

6/12/2009 10:13:52 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Patrick Marroum CDER/OPS/ONDQA

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Don Henry
Project Manager, ONDQA, 301-796-4227 on behalf of Martha Heimann

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 20, 2009		22-462	NDA submission	March 27, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Baclofen (intrathecal)	standard	Neurology	July 20, 2009

NAME OF FIRM: CNS Therapeutics

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☒ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☒ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☒ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The applicant has requested a waiver of the bioequvialency study. A copy of the submission will be forwarded.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
{See appended electronic signature page}	☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ramesh Sood

4/20/2009 03:33:30 PM